REMARKS

This Amendment cancels claim 24, amends claims 23 and 25, and adds new claim 33. The 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole of claim 23 is taken from canceled claim 24. One of ordinary skill in the art would understand "oromucosal adminstration" to mean all or substantially all the active ingredient is absorbed via oral mucosa. The amendment of claim 25 merely changes its dependency to claim 23. New claim 33 is supported by page 2, line 30. Claims 23 and 25-33 are pending.

A Request for Continued Examination (RCE) is attached. Entry of this Amendment is requested.

Examiner's Gembeh and Hayes are thanked for the courtesies extended to Dr. Savola and the undersigned during a personal interview held January 12, 2008. The Examiner Interview Summary Record accurately reflects the substance of the interview.

The 35 U.S.C. § 103(a) rejection of claims 23-32 over U.S. Patent No. 5,498,623 to Karjalainen et al. in view of U.S. Patent No. 5,658,938 to Geerts et al., U.S. Patent No. 6,326,401 to Chauveau et al., Huupponen et al., 58 Clin.Pharmacol.Ther. 506-11 (1995) and U.S. published application US 2004/0236108 to Smith et al., is traversed. The claimed method of administration requires

a formulation containing fipamezole [4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole or its acid salt] to be administered to a patient by oromucosal administration, defined as absorption via oral mucosa.

Applicants maintain and incorporate herein their previous arguments regarding the failure of the cited references to raise a *prima facie* case of obviousness against the claimed method. Moreover, even assuming, arguendo, a *prima facie* case of obviousness has been raised, the unexpected results achieved by oromucosal administration of fipamezole rebut the *prima facie* case and demonstrate the patentability of the claimed method.

A Rule 132 declaration is attached, and reports the actual data generated in the studies summarized in Example 8 of the application. In short, oral administration of fipamezole to dogs prolongs the QTc time interval (an important cardiac safety assessment) at systemic concentrations of about 2000 ng/ml. See Fig. 1 of the declaration. In contrast, oromucosal administration (buccal spray) of fipamezole did not cause QTc prolongation, even at systemic concentration levels of up to 3,300 ng/ml. See Fig. 2 of the declaration.

I. Significance of QTc Interval Prolongation

Cardiac conductivity can be monitored by electrocardiograph (ECG), in which the electrical activity of the heart is recorded over time, usually in a noninvasive method via skin electrodes in man and other species, including the dog. Electrical impulses in the heart travel through the heart muscle where they impart electrical initiation of contraction of the heart. The electrical waves are measured at selectively placed electrodes (electrical contacts) on the skin and displayed, for example, on a paper. The letters P, Q, R, S and T have been specifically assigned to the various deflections of the electrical wave forms. The various intervals between these deflections (such as QRS and QT) are routinely used to draw conclusions on cardiac conductivity and the clinical condition of the heart.[1]

The QT interval (time from the beginning of the QRS complex to the end of the T wave) of the electrocardiogram is a measure of the duration of ventricular depolarization and repolarization. Qtc is the QT interval corrected for heart rate in beats/minute. Of the

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[1]See, for example, Myerburg, ch. 232 "Electrocardiography", Harrison's Internal Medicine 999-1011 (Isselbacher KJ, Adams RD, Braunwald E, Petersdorf RG and Wilson JD eds., McGraw-Hill, 9th ed. 1981)

cardiac safety assessments, QTc interval is of major concern because of its association with delayed ventricular repolarization and consequent risks for fatal arrhythmia (including *torsade de pointes*).

Drugs that prolong the QTc interval lead potentially to fatal cardiac dysrhytmias such as *torsade de pointes*. Several drugs have been withdrawn from the market (e.g., terfenadine, astemizole, cisapride, and grepafloxacin) because they either directly caused electrocardiographic abnormality or resulted in drug-drug interactions that led to unacceptable rates of cardiotoxicity.[2]

Much emphasis has been placed on the potential proarrhythmic effects of pharmaceuticals that are associated with QTc interval prolongation. The FDA, among the other competent authorities, have issued guidance to the industry for its assessment[3]. Based on the implied cardiac safety risk, a finding of potential of a drug to prolong QTc interval in preclinical development typically leads a skilled person in the art to abandon such a compound. In this

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[2]Crouch MA et al., "Clinical relevance and management of drug-related QT interval prolongation," 23 Pharmacotherapy 881-908 (2003).

[3]S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals, FDA, (October 2005).

invention, a preclinical safety assessment resulted in such outcome in a standard oral dosing regimen in the dog. Surprisingly, however, when the compound was dosed using an oromucosal route, QTc interval prolongation as a cardiac safety risk factor could be avoided.

II. Unexpected Nature of the QTc Non-Prolongation Results

Nothing in the cited references suggests oromucosal administration of fipamezole will avoid the problem of compromised cardiac safety associated with oral administration of fipamezole. Accordingly, the results summarized in Example 8 and detailed in the attached declaration would be considered surprising and unexpected by one of ordinary skill in the art.

III. Data Commensurate in Scope with Claims

The data reported in Dr. Savola's declaration is fully commensurate in scope with independent claim 23.

In short, fipamezole has been shown to prolong QTc interval when orally administered to the dog. Conversely, oromucosal administration of fipamezole to the dog does not result in QTc prolongation. One of ordinary skill in the art is given no suggestion that a different administration route would result in different QTc outcomes, and thus would believe such different

outcomes sufficiently surprising and unexpected to demonstrate the patentability of the claimed method. Reconsideration and withdrawal of the obviousness rejection of claims 23-32 are earnestly requested.

A Supplemental Information Disclosure Statement is attached, and submits the documents cited herein to support the significance of QTc prolongation with respect to pharmaceutical development.

It is believed this application is in condition for allowance. Reconsideration and withdrawal of the obviousness rejection of claims 23-32, and issuance of a Notice of Allowance directed to claims 23 and 25-33, are respectfully requested. The Examiner is urged to telephone the undersigned should she believe any further action is required for allowance.

The fees for the RCE and the Extension of Time are being paid electronically today. It is not believed any additional fee is required for entry and consideration of this Amendment.

Nevertheless, the Commissioner is authorized to charge Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

/James C. Lydon/

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Enclosures:
- Petition of Extension of Time
- Declaration Pursuant to 37 C.F.R. § 1.132
- Request for Continued Examination (RCE)
- Supplemental Information Disclosure Statement